DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Received 7/18/08 1:00 PM

Date: JUL 08 2008

From: Consumer Safety Officer, Division of Dietary Supplement Programs , Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: **"N,N'-bis(2-mercaptoethyl)isophthalamide"**

Firm: **CTI Science, Inc.**

Date First Received by FDA: April 7, 2008
90-Day Date: July 6, 2008

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date.

Thank you for your assistance.

Theresa Prigmore

FDA-1995-S-0039

RPT 472

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

Boyd E. Haley, Ph.D
CTI Science, Inc.
119 Burnside Drive
Nicholasville, Kentucky 40365

JUN 17 2008

Dear Dr. Haley:

This is to inform you that the notification, dated February 1, 2008, that you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on April 3, 2008. Your notification concerned the substance you called "N,N'-bis(2-mercaptoethyl)isophthalamide (code name CT-01)" which you identify as new dietary ingredient that you intend to distribute in a dietary supplement product.

According to your notification, "the ingredient will be marketed in capsules containing 25, 50 or 100 mg of CT-01.... [t]he recommended use will be one capsule per day: a 25 mg capsule for children of 55 lbs weight, and the 50 and 100 mg capsules for adults based on human body weight. The 50 mg capsule will be for individuals weighing between 40 and 100 pounds and the 100 mg capsule will be for adults weighing 100 to greater than 200 pounds. As a precautionary matter, the labeling will recommend against use by (i) pregnant and lactating women and (ii) children under 4 years of age or under 55 pounds."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C.350 b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

It is unclear on what basis you assert that "N,N'-bis(2-mercaptoethyl)isophthalamide" that is the subject of your notification is a "dietary ingredient" within the meaning of 21 U.S.C.

321(ff)(1) that may be lawfully used in dietary supplements. A dietary supplement means, among other things, a "product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:
(A) a vitamin;
(B) a mineral;
(C) an herb or other botanical;
(D) an amino acid;
(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)."
FDA requests that you submit information explaining your basis for asserting "N,N'-bis(2-mercaptoethyl)isophthalamide" falls under the definition of dietary ingredient in 21 U.S.C. 321(ff)(1).

In addition, your notification states on page 8 that [t]here may be enzymes that could hydrolyze the amide linkage producing the two products shown below." This statement is followed by a discussion of the safety of isophthalic acid (1,3 dicaroboxybenzoate) and cysteamine.

The statutory definition of dietary supplement includes 21 U.S.C. 321(ff)(3), which includes and excludes from the definition of dietary supplement certain "articles" based on their regulatory and marketing history. While the term dietary supplement "does include an article that is approved as a new drug under section 505...and was, prior to such approval...marketed as a dietary supplement or as a food" (21 U.S.C. 321(ff)(3)(A)), the term dietary supplement does

> not include an article that is approved as a new drug under section 505...or an article authorized for investigation as a new drug...for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval...or authorization marketed as a dietary supplement or as a food. 21U.S.C. 321(ff)(3)(B).

In order to determine the eligibility of "N,N'-bis(2-mercaptoethyl)isophthalamide" to be a dietary supplement, FDA requests that you provide information as to whether "N,N'-bis(2-mercaptoethyl) isophthalamide" may be used as a dietary source of cysteamine.

In addition, the conditions of use stated in your notification are unclear. According to your notification, "The 50 mg capsule will be for individuals weighing between 40 and 100 pounds..." but "the labeling will recommend against use by ... children under 4 years of age or under 55 pounds, You are thus recommending the 50 mg capsules for for children over 4 years old and between 55 and 100 lb and also for *adults weighing between 40 and 100 lb* (emphasis added). The only individuals between 40 and 55 lb identified by your recommendations are adults in that weight range. FDA requests that you clarify the populations that are the intended consumers of this product and basis for your determination of the appropriate serving levels for each of those populations.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that your "N,N'-bis(2-mercaptoethyl)isophthalamide" will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of April 3, 2008. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter please contact me at (301) 436-1448.

Sincerely yours,

Linda S. Pellicore

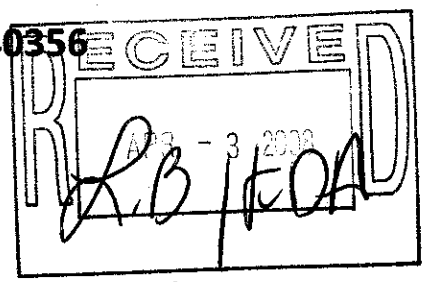
Linda S. Pellicore, Ph.D.
Supervisor, Senior Toxicologist
New Dietary Ingredients Review Team
Division of Dietary Supplement Programs
Office of Nutrition, Labeling
and Dietary Supplements
Center for Food Safety and Applied Nutrition

533

CTI Science, Inc.

119 Burnside Drive

Nicholasville, KY 40356



February 1, 2008

Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-455)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

Notice is hereby given pursuant to the requirement of Section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act of the intent of CTI Science, Inc. to introduce a new dietary ingredient for use as an antioxidant, N,N'-bis(2-mercaptoethyl)isophthalamide (code name CT-01), into interstate commerce on or after 15 June 2008. This notification is provided in the format specified in 21 C.F.R. 190.6(b).

CT-01 has been extensively tested using both independent commercial toxicity testing facilities and academic research laboratories. No toxic effects to organs have been identified in 28 day exposure to rats at extremely high levels compared to the recommended human daily use. Test reports show a positive oxygen radical absorbance capacity (ORAC) test and a negative Ames mutagenicity result. All final test reports are attached as appendices. Raw data will be submitted upon request.

Pursuant to 21 CFR 20.60-61, CTI Science, Inc. requests that this information be kept confidential and not be publicly disclosed.

Sincerely,
CTI Science, Inc.

Boyd E. Haley, PhD
President
Professor of Chemistry and Biochemistry
University of Kentucky

2008-2357

42 TABLE of CONTENTS

43 Premarket Notification for N,N'-bis(2-mercaptoethyl)isophthalamide (code name CT-01) by CTI
44 Science, Inc.

A. Test Article Characterization Information

B. MB Research Report on UP/DOWN Study in Rats

C. MB Research Final Report on 28 day Rat Toxicity Trial

   i. Method Development by ABSORPTION SYSTEMS

   ii. Lab Diet

   iii. Ophthalmoscopic Examination Report

   iv. Research Pathology Histology Report

   v. MB Research Laboratories Standard Protocol 1050A

D. Mutagenic Study Report

E. INNOVABIO ORAC Report

F. Stability Studies of Stored CT-01

G. MSDS Sheets on Isophthalic Acid and Cysteamine

PREMARKET NOTIFICATION FOR A NEW DIETARY INGREDIENT

1. **Manufacturer Identity:** CTI Science, Inc.
   11 9 Burnside Drive
   Nicholasville, KY 40356

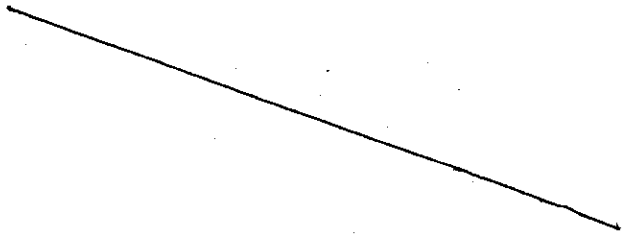
2. **Dietary Ingredient Name:** N,N'-bis(2-mercaptoethyl)isophthalamide (CT-01)

3. **Description of NDI Product:** CT-01 is a pure white, free flowing powder. The purity and quality of the final product are monitored by HPLC, two types of thin layer chromatography (TLC), infrared spectrometry (IR, to show only –SH and no –S-S- signals), sulfhydryl content by dithiolnitrobenzoic acid (DTNB) analysis, and with mass of compound confirmed by mass spectrometry (MS). Using these techniques, no impurities can be detected. We calculate that the NDI is at least 98% CT-01 based on the detection of the HPLC separated materials. The chemical characterization and analytical methods prepared by an independent laboratory, Absorption Systems, for MB Research in conjunction with the 28 day toxicity test is abstracted in Part 4 (II)(ii) below and presented in its entirety in Appendix C, Section 1.

   I. **The Level of the NDI in a Dietary Supplement:** The ingredient will marketed in capsules containing 25, 50 or 100 mg of CT-01. We will claim only that CT-01 is an antioxidant.

   II. **The Conditions of Use:** The recommended use will be one capsule per day: a 25 mg capsule for children over 55 lbs weight, and the 50 and 100 mg capsules for adults based on human body weight. The 50 mg capsule will be for individuals weighing between 40 and 100 pounds and the 100 mg capsule will be for adults weighing 100 to greater than 200 pounds. As a precautionary matter, the labeling will recommend against use by (i) pregnant and lactating women and (ii) children under 4 years of age or under 55 pounds weight.

   III.



pages 5 through 8

4 PAGES TOTAL

REDACTED IN ITS

ENTIRETY

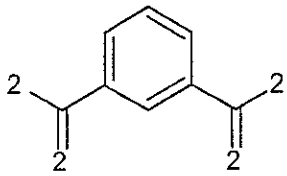
CONTAINS

TRADE SECRET

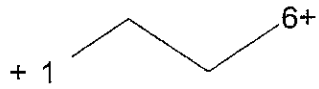
CONFIDENTIAL

COMMERICAL

INFORMATION



Isophthalic acid



cysteamine

VIII: <u>The B-cell Hyperplasia Seen in Rats Treated with CT-01</u>:

Normally, B-cell hyperplasia is seen as an immune system response to a diseased state such as various cancers, viral infections, or autoimmune disorders of unknown cause. The rats in the 28 day toxicity trial had none of these afflictions so the mild to moderate B-cell proliferation at high CT-01 levels had to have another origin. It is most likely due to the antioxidant properties that have been seen to produce this effect. In a complete literature search on B-cell hyperplasia, not one immunotoxicant was found that causes this. Most immunotoxicants cause an atrophy of the spleen or thymus and a decrease in B-cell production.

B-cell proliferation or hyperplasia is controlled by a complex cytokine and receptor system. According to published studies (Molecular Mechanisms Guiding Late Stages of B-cell Development. A.G. Rolink, J. Andrsson and F. Melchers Immunological Reviews 2004 197:41-50) "in mice large numbers of immature B-cells are continuously produced in the bone marrow. To enter pools of mature B cells, these immature B cells have to pass two checkpoints. First, B cells have to migrate from the bone marrow to the spleen. The second checkpoint involves the immature B cells differentiating to mature B cells within the spleen. As the net result of this selection and maturation, only a fraction of the newly produced B cells enter the mature B-cell pool." This review describes the complex involvement of several surface receptors (CD-19, 21, 23, sIgM). They also suggest that only 10-20% of the immature B cells enter the spleen and only 5-10% of immature B-cells become long-lived mature B-cells. They then speculate on the huge number of possible causes for this high level of B cell loss indicating that the nature of this is not known but state that a crucial role for a new member of the TNF (tumour necrosis factor) family of ligands is involved called BAFF (B-cell activating factor). BAFF over expression leads to B-Cell hyperplasia and deletion of BAFF leads to hypoplasia.

Another review (Peripheral B-Cell Maturation: The Intersection of Selection and Homeostasis. M.P. Cancro, Immunological Reviews 2004, 197: 89-101) states "Because B-linage commitment is not regulated by peripheral pool size and most peripheral B cells are quiescent, the primary factors governing steady-state numbers are the

proportion of immature B cells surviving transit through later developmental stages and the longevity of mature B cells themselves." He also states that "Signaling through one of the B-lymphocyte receptors controls B-cell numbers in two ways: by varying the proportion of cells that complete transitional B-cell development and by serving as the primary determinant of mature B-cell longevity." It is also thought that B-Cells complete maturation after migrating to the periphery.

What is obvious is that B-Cell hyperplasia is controlled by biological processes that could easily respond in a positive or negative manner to various compounds at either the transitory path or the maturation process. An increased level of oxidative stress is known to have a major negative effect on immune function. That CT-01 induced B-cell hyperplasia represents an immune stimulation by an antioxidant, and not a toxic event, is supported by the research literature in this area.

A review (Immunotoxicology Assessment in the Pharmaceutical Industry. J.H. Dean, J.R. Hincks and B. Remandet Toxicology Letters 1998:102-103; 247-255) describes the most used immunotoxicology assessments used by American pharmaceutical industries for testing new molecular entities (NMEs) during preclinical development. They state that "The decision on evaluating a compound was overwhelmingly [91%] based on a case – by-case review with the decision driven by a change during routine toxicity studies in one or more hematology parameters [CBC], or a change in lymphoid organ weight, cellularity, or histopathology [55% of time]." With CT-01, no significant organ weight change occurred and no cellularity or histopathology was reported at 1,000 mg/kg body weight.

In studying known immunotoxins, Dean et al. remarked that the most significant impact of immunotoxicants was on lymphocyte sub-populations with B cells being much more sensitive than the other subtypes. With cyclosporine both immunostimulation and immunosuppression were observed at 5 mg/kg body weight of cyclosporin. The authors suggest that immunostimulation occurred at lower cyclosporine concentrations as suggested by B-Cell hyperplasia. At the higher dosage (20 mg/kg body weight), immunosuppression occurred and all lymphocyte parameters were depressed. This would include B-cell production.

The total lack of any observable tissue changes indicating toxicity in all of the other organs of the body shows that CT-01 is not toxic to tissues in general or to the spleen. The significant antioxidant properties of CT-01 at extremely high concentrations induced the B-cell hyperplasia, as also observed in the experiments using high levels of cocoa, as referenced below. This B-cell hyperplasia is attributed to cocoa's antioxidant properties.

Extraction of the tabular data from the histopathology report concerning hyperplasia in the spleen is presented below from page 11 of the 28 day toxicology report. See Appendix C Section (iv). It shows that only two rats in the 0.5g/kg body weight showed mild atrophy of the spleen and none in the 1.0g.kg body weight. This indicates CT-01 is not the cause of this atrophy. The lymphoid cell hyperplasia was minimal (21 rats), mild (13 rats), and moderate (8 rats), and none in the high or severe range. Seven of the 8 rats with moderate hyperplasia were in the highest dose range. It is important to note that this minimal to moderate hyperplasia takes place at dosage levels that are exceptionally high compared to the recommended amount of CT-01 to be taken daily by humans. No high or severe levels of hyperplasia were observed.

Spleen:	males				females			
No. Examined	10	10	10	10	10	10	10	10
CT-01 g/kg bw	0	.1	.5	1.0	0	.1	.5	1.0
No. Normal	10	7	3	0	10	6	0	0
Atrophy	[0]	[0]	[1]	[0]	[0]	[0]	[1]	[0]
Mild	0	0	1	0	0	0	1	0
Hyperplasia,								
Lymphoid cell	[0]	[3]	[7]	[10]	[0]	[4]	[9]	[9]
Minimal	0	3	5	2	0	4	5	2
Mild	0	0	2	5	0	0	3	3
Moderate	0	0	0	3	0	0	1	4

That the observed hyperplasia is the result of immune activation at high doses, instead of toxicity, is supported is by the fact there were no significant weight loss or gains in the spleens of CT-01 treated animals, or in any other tissues, including the thymus, as would be expected if toxicity were involved. Only two mild weight change atrophies were noted in the 30 rats exposed to CT-01, and these two mild atrophies were not in the highest dosage levels indicating that CT-01 is not the cause. This strongly supports the conclusion that weak immune system activation, not toxicity, was the cause.

In all of the histology of the CT-01 treated rats, there were no reports of tissue damage, such as spleen atrophy, as reported in many other articles on immunotoxins. The activation of the immune system as evidenced by B cell proliferation is a property of some natural foods such as cocoa as presented below.

De Wall, E.J. et al. Differential effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin, bis(tri-n-butytin)oxide and cyclosporine on thymus histophysiology. CRC critical Reviews of

Toxicology 1997;27: 381-430. This paper, as referenced in the 2004 Vos and Kuper paper below, showed that most immunotoxic/thymotoxic compounds induce atrophy of the organ as a result of lymphocyte depletion of the cortex. This did not happen with CT-01. No weight loss or toxic effects were seen even at the 1,000 mg/kg body weight. In fact, in Table 1 continued on page 11 and 12 of Appendix E (page E13 of E113), there were no thymus abnormalities that correlated to CT-01 levels.

Ezendam, J. et al. Hexachlorobenzene-induced immunopathology in Brown Norway Rats is partly mediated by T cells. Toxicological Sciences 2004, 78; 88-95. In this study, hexachlorobenzene (HCB), which is known to have pronounced effects on the immune system, was fed to rats in a diet that contained 450mg/kg feed. Using the factor 0.00054 determined above, the daily exposure was approximately 0.243mg/kg body weight/day. (This is an estimate, as both used young rats, but the weights were not specifically given.) Within 10 days, severe skin lesions appeared on the rats. The level of CT-01 given by gavage to rats was 100, 500, and 1,000 mg/kg body weight/day or between 411 and 4,115 times greater, and no significant skin or other body lesions were observed. Thus, CT-01 even at exceptionally high exposures does not cause the problems associated with an immunotoxin but is likely a weak immune activating system.

Vos, J.G and Kuper, C. F. Chemically-Induced Immunopathology and Immune Functional Changes. J. Toxicol. Pathol. 2004, 17; 137-146. These authors state that "In assessing immunotoxicity, a two-tier testing system is usually employed in rodent in which the first tier is a general screen for (immune)toxicity including enhanced histopathology of lymphoid organs and the second tier consists of more specific immune function studies including host resistance tests or mechanistic studies." Studies with the immunotoxicants TCDD, TBTO, HCB, azathioprine, and cyclosporine A are discussed, which provide data correlating histopathology with immune function changes. What is important is the amount of these immunotoxicants compared to the amount of CT-01 used in the 28 day study. For example, these researchers exposed rats to a diet of 0, 0.5, 5, or 50 milligrams TBTO/kg, a diet level which had induced immune function suppression in an earlier short term study. CT-01 was given for 28 days at 100, 500, and 1,000 mg/kg body weight by direct gavage. To get to the lowest exposure of CT-01, a rat on the 50mg TBTO/kg diet would have to eat two kilograms (4.4 pounds) of food per day, which is not possible. The levels of CT-01 given would destroy the immune system of a rat if CT-01 were a significant, even low potency immunotoxicant. The TDI (tolerable daily intake) of these immunotoxicants set by WHO was 0.27 micrograms/kg/day for TBT, based on a dietary effect of 0.5mg (or 500 micrograms) TBT/kg diet. For CT-01 the highest and lowest exposures were 100,000 and 1,000,000 micrograms/kg body weight/day. This is enormously higher than the exposure to TBT that would cause immunotoxicity.

T Germolec, D.R. et al. The accuracy of extended histopathology to detect immunotoxic chemicals. Toxicological Sciences, 2004, 82, 504-510 and Germolec, D. R. et al. Extended histopathology in immunotoxicity testing: Interlaboratory Validation Studies. 2004 Toxicol. Sci.78, 107-115 These two papers are important as they discuss the latest attempts to define the reliability of histopathological tests to detect immunotoxic chemicals in mice. A quote in the abstract of one of the papers (2004, v82, 504-510) defines the situation: "When moderate to marked histopathological changes were used to identify immunotoxic chemicals, the level of accuracy that could be achieved was poor." Thus, histological changes in the spleen or thymus are not yet a reliable way to determine what is or is not immunotoxic. They also state that the conclusions drawn by practicing histologists are not in good agreement. The histological identification of B-cell proliferation is likely caused by the reducing capability of CT-01 at high doses. With no significant weight changes in the spleen or thymus, this proliferation is not a toxic event.

Several publications have shown that healthy foods contain substances that enhance the antioxidant properties of cells in living rats and also modulate the lymphocyte composition. The most relevant of these are summarized below with their conclusions.

Emma Ramiro-Puig et al. J. Agric. Food Chem. 2007, 55, 6431-6438. Cocoa-Enriched Diet Enhances Antioxidant Enzyme Activity and Modulates Lymphocyte Composition in Thymus from Young Rats. Excerpts from paper: "Cocoa is a rich source of flavonoids and procyanidins and this article reports the effect of continuous cocoa intake on antioxidant capacity in plasma and tissues, including lymphoid organs and liver, from rats. Cocoa enhanced total antioxidant capacity in all tissues but especially in thymus. A hierarchy in reducing activity was observed: thymus> spleen> liver." This was attributed to flavonoid accumulation in specific target tissues allowing a maintained enhancement of their antioxidant capacity. "The influence of cocoa on thymus antioxidant activity led us to believe that cocoa could also affect lymphocyte composition as we previously found in spleen and gut-associated lymphoid tissue (GALT) (see reference 40 *Ramiro-Puig et al. Spleen Lymphocyte Function Modulated by a Cocoa Enriched Diet. Clin. Exp. Immunol. In press).* "

The effects on thymus and spleen total antioxidant capacity (TAC) to cocoa were found not to be significantly dose-dependent. The authors state that one possible reason for this fact (the TAC observations) may be the activation of oxidative pathways in thymus and spleen as a cell compensatory mechanism triggered by high levels of antioxidant accumulated in those tissues. On the other hand, DN cells, a subset whose proportion was also increased by cocoa diet, have multi-lineage potential, including B cells, T cells, myeloid cell, natural killer cells, and dendritic cells. See their reference 41: *Sanbongi, C. et al. Polyphenols in chocolate, which have antioxidant activity, modulate immune functions in humans in vitro. Cell Immunol. 1997, 177, 129-136* and *Ramiro, E. et al.*

Flavonoids from Theobroma cacao down-regulate inflammatory mediators. J. Agric. Food Chem. 2005, 53 8506-8511. These papers showed the inhibitory effects of cocoa flavonoids on reactive oxygen species (ROSs) production from activated immune cells. In summary, a cocoa diet enhances thymus and immune system antioxidant defenses and influences thymocyte and other immune cell differentiation. The strong antioxidant properties of CT-01 could be expected to do the same at the high concentrations used in the 28 day rat feeding study, but this influence on the spleen and immune cell hyperplasia is not a toxic event.

IX. Risk Assessment:

The toxicity testing on CT-01 was done at levels much higher than would be recommended for human usage. The CT-01 will be packaged in 25, 50, and 100 mg capsules and recommended to be taken at levels dependent on the person's body weight. Dividing a person's weight in pounds by 2.2kg/lb will give the kg body weight. Dividing the 0.025, 0.050, and 0.10 grams CT-01 per capsule by the human kgs body weight shows that the recommended dosages are considerably below the levels tested which caused no toxicity in the test animals. For example, fifty five lbs. is 25 kg and the 25 mg capsule recommended would be 0.0010 grams/kg body weight at this level of use in a small child. This is 100 fold less than the lowest levels used in the 28 day rat toxicity trial. We will recommend that children under 4 years of age or under 55 pounds not take CT-01. As the weight of the major users, much older individuals, increased the ratio would be as low or even lower. For example, a 154 lb (70 kg) person taking the maximum recommended 100 mg capsule would be exposed to 0.00145 grams CT-01/kg body weight. This is likely quite safe concerning the greater than 5 grams/kg LD_{50} of CT-01. Dividing 5.0/0.00145 gives a factor of 3,448 times less than the 5 gram/kg body weight amount that did not cause any lethality or detectable organ damage in rats. The 0.00145 grams/kg body weight is also 690 times less than the 1.0 gram/kg body weight given to rats in the 28 day toxicity testing. The following table shows the grams/kg body weight for the recommended dosages of CT-01. All of the recommended dosages are at least 100 times lower than the lowest tested level of CT-01 in the 28 day toxicity testing.

Subject Body Weight		**Grams CT-01 per Gram Body Weight**		
		Milligrams CT-01 in Capsule		
Lbs	Kg	25mg (.025g)	50mg (.050g)	100mg (.10g)
55	25.0	0.00100	0.0020	0.0040 g/kg
60	27.3	0.00091	0.0018	0.0037
88	40.0	0.00063	0.0013	0.0025
132	60.0	0.00042	0.0008	0.0017
176	80.0	0.00031	0.0006	0.0013
220	100	0.00025	0.0005	0.0010

We had studies done on pregnant rats to determine if CT-01 was safe to use in pregnant and lactating women. No detectable harmful results were identified. However, as a precautionary measure we are recommending that CT-01 not be taken by pregnant or lactating women.

The studies on mutagenicity showed that CT-01 was without mutagenic capability as would be expected for a compound with chemistry suggestive of antioxidant properties. The positive ORAC test also supported the concept that CT-01 is not capable of mutagenic chemistry and, in fact, would likely protect against any mutagenesis caused by hydroxyl radical formation.

The chemical stability of CT-01 is one of its strongest properties. It is stable for extended periods of time at room temperatures even when dissolved in solutions, such as DMSO, that would encourage oxidation. In the ORAC study it was demonstrated that CT-01 is an effective hydroxyl radical scavenger. This would allow CT-01 to be effective for reducing oxidative stress by reducing the needed hydroxyl radical scavenging by reduced glutathione.

CT-01 represents a stable, non-toxic, hydroxyl radical scavenger. This is the basis of its antioxidant properties as it would conserve the naturally produced reduced glutathione by aiding in removal of hydroxyl radicals.

X. Summary:

CT-01 has an acute oral toxicity level of greater than 5 grams/kg body weight when given orally to rats. Subchronic oral toxicity was tested using CT-01 for 28 straight days at 0.1, 0.5, and 1.0 grams/kg body weight in rats. This caused no lethality and no damage to any organs. The value of CT-01 is as an antioxidant. At the higher dosages no damage to any organs was observed by histological procedures. Only a mild to moderate B-cell proliferation occurred at these elevated levels that is due to a mild immune system activation by the significant antioxidant properties of CT-01. This proliferation effect on immune cells has been observed with other nutritional antioxidants such as cocao and other foods high in flavoniods.

APPENDICES A THROUGH F

REDACTED IN ITS
ENTIRETY
CONTAINS
TRADE SECRET
CONFIDENTIAL
COMMERICAL
INFORMATION

APPENDIX G

MATERIAL SAFETY DATA SHEET

Date Printed: 04/01/2008
Date Updated: 09/07/2006
Version 1.6

Section 1 - Product and Company Information

Product Name	CYSTEAMINE HYDROCHLORIDE
Product Number	M6500
Brand	SIGMA
Company	Sigma-Aldrich
Address	3050 Spruce Street SAINT LOUIS MO 63103 US
Technical Phone:	800-325-5832
Fax:	800-325-5052
Emergency Phone:	314-776-6555

Section 2 - Composition/Information on Ingredient

Substance Name	CAS #	SARA 313
2-AMINOETHANETHIOL HYDROCHLORIDE	156-57-0	No

Formula C2H7NS.ClH

Synonyms Bekaptan * Cysteamine hydrochloride * Cysteaminhydrochlorid (German) * Ethylamine, 2-mercapto-, hydrochloride * beta-Mercaptoaethylamin chlorhydrat (German) * Mercaptoethylamine hydrochloride * beta-Mercaptoethylamine hydrochloride * 2-Mercaptoethylamine hydrochloride * USAF EE-3

RTECS Number: KJ0200000

Section 3 - Hazards Identification

EMERGENCY OVERVIEW

Harmful.
Harmful if swallowed.

HMIS RATING

HEALTH: 1
FLAMMABILITY: 0
REACTIVITY: 1

NFPA RATING

HEALTH: 1
FLAMMABILITY: 0
REACTIVITY: 1

For additional information on toxicity, please refer to Section 11.

Section 4 - First Aid Measures

ORAL EXPOSURE

If swallowed, wash out mouth with water provided person is conscious. Call a physician.

INHALATION EXPOSURE

If inhaled, remove to fresh air. If not breathing give artificial respiration. If breathing is difficult, give oxygen.

DERMAL EXPOSURE
In case of skin contact, flush with copious amounts of water for at least 15 minutes. Remove contaminated clothing and shoes. Call a physician.

EYE EXPOSURE
In case of contact with eyes, flush with copious amounts of water for at least 15 minutes. Assure adequate flushing by separating the eyelids with fingers. Call a physician.

Section 5 - Fire Fighting Measures

FLASH POINT
N/A

AUTOIGNITION TEMP
N/A

FLAMMABILITY
N/A

FIREFIGHTING
Protective Equipment: Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.
Specific Hazard(s): Emits toxic fumes under fire conditions.

Section 6 - Accidental Release Measures

PROCEDURE TO BE FOLLOWED IN CASE OF LEAK OR SPILL
Evacuate area.

PROCEDURE(S) OF PERSONAL PRECAUTION(S)
Wear self-contained breathing apparatus, rubber boots, and heavy rubber gloves.

METHODS FOR CLEANING UP
Sweep up, place in a bag and hold for waste disposal. Avoid raising dust. Ventilate area and wash spill site after material pickup is complete.

Section 7 - Handling and Storage

HANDLING
User Exposure: Do not breathe dust. Avoid contact with eyes, skin, and clothing. Avoid prolonged or repeated exposure. Handle under argon.

STORAGE
Suitable: Keep tightly closed.
Store at 2-8°C

SPECIAL REQUIREMENTS
Hygroscopic.

Section 8 - Exposure Controls / PPE

ENGINEERING CONTROLS
Safety shower and eye bath. Mechanical exhaust required.

PERSONAL PROTECTIVE EQUIPMENT

Respiratory: Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU). Where risk assessment shows air-purifying respirators are appropriate use a dust mask type N95 (US) or type P1 (EN 143) respirator.
Hand: Compatible chemical-resistant gloves.
Eye: Chemical safety goggles.

GENERAL HYGIENE MEASURES

Wash thoroughly after handling.

Section 9 - Physical/Chemical Properties

Appearance	Physical State: Solid Color: Colorless Form: Fine crystals

Property	Value	At Temperature or Pressure
Molecular Weight	113.61 AMU	
pH	3.5 - 5.0	
BP/BP Range	N/A	
MP/MP Range	67.0 - 71.0 °C	
Freezing Point	N/A	
Vapor Pressure	N/A	
Vapor Density	N/A	
Saturated Vapor Conc.	N/A	
SG/Density	N/A	
Bulk Density	N/A	
Odor Threshold	N/A	
Volatile%	N/A	
VOC Content	N/A	
Water Content	N/A	
Solvent Content	N/A	
Evaporation Rate	N/A	
Viscosity	N/A	
Surface Tension	N/A	
Partition Coefficient	N/A	
Decomposition Temp.	N/A	
Flash Point	N/A	
Explosion Limits	N/A	
Flammability	N/A	
Autoignition Temp	N/A	
Refractive Index	N/A	
Optical Rotation	N/A	
Miscellaneous Data	N/A	
Solubility	Solubility in Water:1 M in H2O, 20°C complete, colorless	

N/A = not available

Section 10 - Stability and Reactivity

STABILITY

Stable: Stable.
Conditions to Avoid: Moisture.
Materials to Avoid: Strong oxidizing agents.

HAZARDOUS DECOMPOSITION PRODUCTS

Hazardous Decomposition Products: Carbon monoxide, Carbon dioxide, Nitrogen oxides, Sulfur oxides, Hydrogen chloride gas.

HAZARDOUS POLYMERIZATION
Hazardous Polymerization: Will not occur

Section 11 - Toxicological Information

ROUTE OF EXPOSURE
Skin Contact: May cause skin irritation.
Skin Absorption: May be harmful if absorbed through the skin.
Eye Contact: May cause eye irritation.
Inhalation: May be harmful if inhaled. Material may be irritating to mucous membranes and upper respiratory tract.
Ingestion: Harmful if swallowed.

SIGNS AND SYMPTOMS OF EXPOSURE
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

TOXICITY DATA

Oral
Mouse
1352 mg/kg
LD50

Intraperitoneal
Mouse
250 MG/KG
LD50

CHRONIC EXPOSURE - MUTAGEN

Species: Mouse
Route: Intraperitoneal
Dose: 200 MG/KG
Mutation test: Micronucleus test

Species: Rat
Dose: 5 MG/L
Cell Type: liver
Mutation test: Cytogenetic analysis

Section 12 - Ecological Information

No data available.

Section 13 - Disposal Considerations

APPROPRIATE METHOD OF DISPOSAL OF SUBSTANCE OR PREPARATION
Contact a licensed professional waste disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Observe all federal, state, and local environmental regulations.

Section 14 - Transport Information

DOT
Proper Shipping Name: Aviation Regulated Solid, N.O.S.
UN#: 3335
Class: 9
Packing Group: Packing Group III

Hazard Label: Class 9
PIH: Not PIH

IATA
Proper Shipping Name: Aviation Regulated Solid, N.O.S.
IATA UN Number: 3335
Hazard Class: 9

Section 15 - Regulatory Information

EU ADDITIONAL CLASSIFICATION
Symbol of Danger: Xn
Indication of Danger: Harmful.
R: 22
Risk Statements: Harmful if swallowed.

US CLASSIFICATION AND LABEL TEXT
Indication of Danger: Harmful.
Risk Statements: Harmful if swallowed.

UNITED STATES REGULATORY INFORMATION
SARA LISTED: No
TSCA INVENTORY ITEM: Yes

CANADA REGULATORY INFORMATION
WHMIS Classification: This product has been classified in accordance with the hazard criteria of the CPR, and the MSDS contains all the information required by the CPR.
DSL: Yes
NDSL: No

Section 16 - Other Information

DISCLAIMER
For R&D use only. Not for drug, household or other uses.

WARRANTY
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Inc., shall not be held liable for any damage resulting from handling or from contact with the above product. See reverse side of invoice or packing slip for additional terms and conditions of sale.

MATERIAL SAFETY DATA SHEET

Date Printed: 04/01/2008
Date Updated: 02/05/2006
Version 1.4

Section 1 - Product and Company Information

Product Name	ISOPHTHALIC ACID
Product Number	59200
Brand	FLUKA
Company	Sigma-Aldrich
Address	3050 Spruce Street SAINT LOUIS MO 63103 US
Technical Phone:	800-325-5832
Fax:	800-325-5052
Emergency Phone:	314-776-6555

Section 2 - Composition/Information on Ingredient

Substance Name	CAS #	SARA 313
ISO-PHTHALIC ACID	121-91-5	No

Formula	C8H6O4
Synonyms	Acide isophtalique (French) * Benzene-1,3-dicarboxylic acid * m-Benzenedicarboxylic acid * Isophthalate * Kyselina isoftalova (Czech) * m-Phthalic acid
RTECS Number:	NT2007000

Section 3 - Hazards Identification

EMERGENCY OVERVIEW
Target organ(s): Kidneys.

HMIS RATING
HEALTH: 0*
FLAMMABILITY: 0
REACTIVITY: 0

NFPA RATING
HEALTH: 0
FLAMMABILITY: 0
REACTIVITY: 0

*additional chronic hazards present.

For additional information on toxicity, please refer to Section 11.

Section 4 - First Aid Measures

ORAL EXPOSURE
If swallowed, wash out mouth with water provided person is conscious. Call a physician.

INHALATION EXPOSURE
If inhaled, remove to fresh air. If breathing becomes difficult, call a physician.

DERMAL EXPOSURE
In case of contact, immediately wash skin with soap and copious amounts of water.

EYE EXPOSURE
In case of contact with eyes, flush with copious amounts of water for at least 15 minutes. Assure adequate flushing by separating the eyelids with fingers. Call a physician.

Section 5 - Fire Fighting Measures

FLASH POINT
N/A

AUTOIGNITION TEMP
648 °C

FLAMMABILITY
N/A

EXTINGUISHING MEDIA
Suitable: Water spray. Carbon dioxide, dry chemical powder, or appropriate foam.

FIREFIGHTING
Protective Equipment: Wear self-contained breathing apparatus and protective clothing to prevent contact with skin and eyes.
Specific Hazard(s): Emits toxic fumes under fire conditions.

Section 6 - Accidental Release Measures

PROCEDURE(S) OF PERSONAL PRECAUTION(S)
Exercise appropriate precautions to minimize direct contact with skin or eyes and prevent inhalation of dust.

METHODS FOR CLEANING UP
Sweep up, place in a bag and hold for waste disposal. Avoid raising dust. Ventilate area and wash spill site after material pickup is complete.

Section 7 - Handling and Storage

HANDLING
User Exposure: Avoid inhalation. Avoid contact with eyes, skin, and clothing. Avoid prolonged or repeated exposure.

STORAGE
Suitable: Keep tightly closed.

Section 8 - Exposure Controls / PPE

ENGINEERING CONTROLS
Safety shower and eye bath. Mechanical exhaust required.

PERSONAL PROTECTIVE EQUIPMENT
Respiratory: Use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU). Respiratory protection is not required. Where protection from nuisance levels of dusts are desired, use type N95 (US) or type P1 (EN 143) dust masks.
Hand: Protective gloves.

Eye: Chemical safety goggles.

GENERAL HYGIENE MEASURES
Wash thoroughly after handling.

Section 9 - Physical/Chemical Properties

Appearance	Physical State: Solid Color: Faintly beige Form: Powder

Property	Value	At Temperature or Pressure
Molecular Weight	166.13 AMU	
pH	N/A	
BP/BP Range	N/A	
MP/MP Range	345 °C	
Freezing Point	N/A	
Vapor Pressure	N/A	
Vapor Density	N/A	
Saturated Vapor Conc.	N/A	
SG/Density	N/A	
Bulk Density	N/A	
Odor Threshold	N/A	
Volatile%	N/A	
VOC Content	N/A	
Water Content	N/A	
Solvent Content	N/A	
Evaporation Rate	N/A	
Viscosity	N/A	
Surface Tension	N/A	
Partition Coefficient	N/A	
Decomposition Temp.	N/A	
Flash Point	N/A	
Explosion Limits	N/A	
Flammability	N/A	
Autoignition Temp	648 °C	
Refractive Index	N/A	
Optical Rotation	N/A	
Miscellaneous Data	N/A	
Solubility	N/A	

N/A = not available

Section 10 - Stability and Reactivity

STABILITY
Stable: Stable.
Materials to Avoid: Strong oxidizing agents, Strong bases.

HAZARDOUS DECOMPOSITION PRODUCTS
Hazardous Decomposition Products: Carbon monoxide, Carbon dioxide.

HAZARDOUS POLYMERIZATION
Hazardous Polymerization: Will not occur

Section 11 - Toxicological Information

ROUTE OF EXPOSURE
Skin Contact: May cause skin irritation.
Skin Absorption: May be harmful if absorbed through the skin.
Eye Contact: May cause eye irritation.

Inhalation: Material may be irritating to mucous membranes and upper respiratory tract. May be harmful if inhaled.
Ingestion: May be harmful if swallowed.

TARGET ORGAN(S) OR SYSTEM(S)
Kidneys.

SIGNS AND SYMPTOMS OF EXPOSURE
To the best of our knowledge, the chemical, physical, and toxicological properties have not been thoroughly investigated.

TOXICITY DATA

Oral
Rat
10400 mg/kg
LD50

Intraperitoneal
Mouse
4200 MG/KG
LD50
Remarks: Nutritional and Gross Metabolic:Changes in:Body temperature decrease. Behavioral:Somnolence (general depressed activity). Behavioral:Excitement.

IRRITATION DATA

Eyes
Rabbit
500 mg
24H
Remarks: Mild irritation effect

Section 12 - Ecological Information

No data available.

Section 13 - Disposal Considerations

APPROPRIATE METHOD OF DISPOSAL OF SUBSTANCE OR PREPARATION
Contact a licensed professional waste disposal service to dispose of this material. Dissolve or mix the material with a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Observe all federal, state, and local environmental regulations.

Section 14 - Transport Information

DOT
Proper Shipping Name: None
Non-Hazardous for Transport: This substance is considered to be non-hazardous for transport.

IATA
Non-Hazardous for Air Transport: Non-hazardous for air transport.

Section 15 - Regulatory Information

US CLASSIFICATION AND LABEL TEXT
US Statements: Target organ(s): Kidneys.

UNITED STATES REGULATORY INFORMATION
SARA LISTED: No
TSCA INVENTORY ITEM: Yes

CANADA REGULATORY INFORMATION
WHMIS Classification: This product has been classified in accordance with the hazard criteria of the CPR, and the MSDS contains all the information required by the CPR.
DSL: Yes
NDSL: No

Section 16 - Other Information

DISCLAIMER
For R&D use only. Not for drug, household or other uses.

WARRANTY
The above information is believed to be correct but does not purport to be all inclusive and shall be used only as a guide. The information in this document is based on the present state of our knowledge and is applicable to the product with regard to appropriate safety precautions. It does not represent any guarantee of the properties of the product. Sigma-Aldrich Inc., shall not be held liable for any damage resulting from handling or from contact with the above product. See reverse side of invoice or packing slip for additional terms and conditions of sale.